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# Considerations About the Result of Histological Examination at Pre-Operative Irradiated Cancer

By

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# 術前照射を受けた胃癌の病理組織学的検査成績に関する考按

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曩きに術前照射を行つた胃癌の摘出標本について組織学的に術前照射の放射線効果を判定し，吾々の行つた術前照射の有効性を実証すると共に放射線生物学的作用とこの組織学的所見より術前照射の至適照射量，手術侵襲期の決定目標等に検討を加えて報告し聊か考按を試みた．

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## Chapter I. Foreword

Prior to perform a surgical intervention, a proper dose of radiation energies should be applied to inhibit the proliferation and metastasis of cancer cells. Accordingly, I had stated in my earlier report by checking the deep-dose distribution at irradiation terms which we had been adapted.

It is considered that an expected aim may be attained both physically and biologically by observing this deep-dose distribution, but furthermore, the degree of disorders must be confirmed by histological reference of cancer cells which is undergone the pre-operative irradiation.

However, according to the rule of radiological irradiation treatment, as large dose as possible should be applied to the cancer tissues, while on other hand, prevent the disorders of surrounding tissues to the minimum, and try to bring a highest degree of change to the cancer cells, such as denaturalization, disruption and/or absorption, but as frequently stated, the proper dose can be determined by the clinical experiences and the

individuals with cancers based on the result of radiobiological studies. That is, we primarily prearranged the skin dose of 2,000r to 3,000r, and devised a method as to be able to apply effectively and in short length of time as possible. At present, we are using the first method of pre-operative irradiation as fundamental that such dose may be applied by a simple dividing method at small radiation field, and then the surgical intervention may be performed of 10 to 15 days after the completion of irradiation.

The histological findings of extirpated cancer, which I intend to report in this thesis, is consequently shows the histological pictures obtained by this method. As a result of histological findings, some changes were shown in the disorders of cancer cells, namely the histological pictures, for which we were much expected, and they were the findings which proved the actual condition of our clinical observations and the result of biological studies as already mentioned.

I, therefore, discuss the problems in sequence with the following chapters, and make an attempt for some considerations according to the radiobiology and the theory of "cancer immunity", which we consider as the fundamental of pre-and post-operative irradiation method, and furthermore, we wish to contribute for the completion of pre-operative irradiation considering upon the existing "irradiation effect judging criterion" from the radiological point of view.

## Chapter II. Literature Considerations

As aforementioned, the number of predecessors who performed in the field of pre- and post-operative irradiation were not always few. However, the fact is, that it has been practised and reported systematically or the report concerning in obtaining the favourable results for the aim of pre-operative irradiation, namely the improvement of surgery result and expansion for the scope of operation suitability, are quite rare and there are no more than few instances throughout all ages and countries.

Fig. 1 Description of Pre-Operative Irradiation

| Description | Purpose of Treatment | Aim for Irradiation | Irradiation Scope | Surgical Operation |
|---|---|---|---|---|
| First method of Pre-Operative Irradiation | Improvement of operation results | Devitalization of cancerous cells. Control of proliferation and metastasis of cancer cells | Tumor of primary cancer | Radical operation |
| Second Method of Pre-Operative Irradiation | Expansion of operation suitability | Zerstoruny of cancer cells. As much cancerousecells as possible to be disrupted and resolved | As wide as possible to the primary cancer and its surrounding | Extirpation of of remaining cancer cells |
| A fundamental type of pre-oerative irradiation is First Method. | | | | |

In my third report, an introduction was already made for the pre-operative irradiation method of gullet cancer, centering by Nakayama Surgery, in which I added a few critisms. However, the histological reference, which were tried to determine proper dose of radiation for pre-operative irradiation, was conducted under the cooperation of Professor

Takizawa, a pathologist, who settled the following "irradiation effect judging criterion" (X) against cancer cells. That is, he divided the irradiation effect (X) into three different categories, such as (a) $X_1$ (proliferation remained) (b) $X_2$ (denaturalized) and (c) $X_3$ (disrupted and/or resolved).

As for your reference, and to clear the ground of the decision for proper dose of irradiation, this judging criterion will be cited hereunder.

Fig. 2.

| Category (X) | Nucleus | Protoplasm | Focus |
|---|---|---|---|
| $X_1$ | Indirect division and multiforms | Although the basic protoplasm is to be observed, vacant tissue denaturalization is partly observed | Proliferation is to be observed |
| $X_2$ | Almost no indirect division but expansion and heavy compression of nucleus are to be observed | Many vacant-tissue denaturalization is to be observed | Denautralized |
| $X_3$ | None of indirect division but many disruptions and resolutions are to be observed | Vacant-tissue denaturalization is to be observed | Disrupted and resolved |

If relationship between the radiation dose of tumor and the change of cancer tissues (X) causes by irradiation may be shown on a graph, the effect of irradiation advances almost parallel to the increase of radiation dose, which may result roughly between $X_2$ and $X_3$ at the doses between 2,000r and 3,000r. That is, it is reported that the restraint effect by irradiation was observed and we were informed that there is no slight obstruction for both the living body and surgery at this dosage.

In regards with the irradiation terms, the focus dose for pre-operative irradiation is to be estimated between 150r and 250r per day and the length of time for irradiation is to be fixed at between 10 and 14 days, and surgical intervention should be performed immediate after the completion of irradiation. A concrete reason of this decision for surgical intervention is due to cancer cells which may cause again its proliferation as time passes. Observing the above treatment schedule, the change of cancer cells aforementioned is the histological findings obtained immediate after the completion of irradiation at the doses of 2,000r-3,000r. However, if consideration is made for the results of our biological studies, and leave some intervals after completion of irradiation as well as our first method, then it is considerable that more distinct denaturalization may appear and makes almost no difference between $X_1$ and $X_2$ or it may leaves $X_3$ only. In case, such development does not occur, the appearance of some other factors is may be considered.

This dose is completely same on the value with that of as already reported as irradiation terms. It is, however, quite natural that it may cause a fair difference in the "way of effect" by the irradiation method and the efficiency of generating apparatuses.

As previously stated, we divided to use this radiation dose by three different appar-

atuses; (1) close irradiation (body cavity tube) (2) common high voltage and, (3) Cobalt 60 gamma rays, depending on the site of cancer and apply the same dose at either apparatus. The irradiation period should be considered at maximum 10 days and its affect is to be observed between 10 and 15 days by the extirpated cancer tissues. Anyway, this irradiation effect judging criterion determined by Professor Takizawa is a meritorious result which brought a guidance to the pre-operative irradiation, together with the improvement of operation result at Nakayama Surgery, and I do not hesitate to express my utmost respect for his achievement.

Depending the effect judgement of pre-operative irradiation on cytological reference of extirpated cancer tissues will be the surest and unanimous method at present medical science. However, when anti-cancerous nature of the individual with cancer and this problem is considered from radiobiological standpoint, it is quite doubtful whether the irradiation effect judgement is fully reliable only by histological pictures of cancer tissues extirpated immediate after the completion of irradiation. It is just because the reduction, disruption and resolution of the irradiated tumor is not always largest in size at the time immediate after the completion of irradiation but it may causes continuous denaturalization and disruption as time goes by.

In the next, Mr. Matsuda and others have fixed the applicable irradiation dose by Cobalt 60γ at 4,000r, which is far exceeds the doses at Nakayama Medical Room as mentioned, and it is reported that the time of surgical intervention should be based of 1 to 2 weeks after irradiation completed. The histological pictures of cancer tissues irradiated over 4,000r were observed as deeply-coloured, metamorphosis, vacant-tissue state with many nucleus or hugeness, and also the denaturalized vacant-tissue state to the protoplasm and the chromatic reduction were observed. These changes were clear in skirrhus-type, less in the adenocarzinom and the solidercarzinom were just sited in the mid of them. Based on the above findings, Mr. Matsuda affirmed the usefulness of pre-operative irradiation by $^{60}$Co γ for the gastric cancer, and consequently, he considered that over 4,000r should be required.

As to see in the above reports, it is needless to mention regarding the essentiality of the pre-operative irradiation and its effect. However, when the various clinical cases to be observed in detail against the cases of these reports, about 60–70% of clinical katar could be noticed and the patients made complaints of nausea, loss of appetite, feeling of weakness, and furthermore, between 70% and 80% of them were accompanied with loss of weight. These facts are quite important and anyone should bear in mind as long as the therapeutic treatment is to be conducted. Besides, these are the cases that both palpation and X-ray pictures were improved more than 60% and their effectiveness as the cancerous treatment was completely confirmed.

With regards to this point, there exist a remarkable difference between the result of our observations as already stated, and one may wonder why such difference should be existed since almost same radiation doses were applied as for the pre-operative irradiation.

As a matter of fact, this doubt is originated from the sensibilty of cancer tissues and the cancerous disposition of the individuals with cancers, and also it is the matter to be influenced by the method and terms of irradiation.

Any suspicious points arise from the abovementioned "Literature Considerations" shall be discussed on the separate chapter "Summary and Discussion" by comparing with the result of our examination.

## Chapter III. Results of Examination

This study had begun since December 1960 under the 5-year plan, however, regarding the biological study which was considered as fundamental, had been started more than

Fig. 3

| Case No. | Name | Age | Diagnosis | Pre-Operative Irradiation (Method and Terms) | No. of days required till operation | Operation Method | Classification of Microscopic Tissues | Histological Findings of Extirpated/Irradiated Cancer Tissues | Effect Judging Criterion | Specimen's No. |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | ♀ Kawamoto | 52 | Gastric Cancer | Close-irradiation 2- fields Per field 600x7=3600r | 16 days | Curative resection | Borrmann Type III | A mucinous Carzinoma. Nucleus denaturalization partly observed | $X_1$ | 72C |
| 2 | ♀ Futjia | 67 | -ditto- | Close-irradiation 2- fields Per field 600x6=3600r | 12 days | -ditto- | -ditto- | A skirrhus. Swell of nucleus and vacant tissue denaturalization of protoplasm observed | $X_1$ | 75A, B |
| 3 | ♀ Ueda | 46 | Rectum Cancer | 200 KVP Apparatus 1- field 200x10=2000r | 12 days | Rectal resection | Localization Tumor type | A columnar Epithetium Cancer Nuclear division observed in cancerous cells and lack of effect | $X_1$ | 94A |
| 4 | ♀ Sasaki | 56 | Gastric Cancer | Close-irradiation 2- fields Per field 600x5=3000r | 17 days | Curative resection | Borrmann Type III | No obvious cancer tissues observed | $X_2$? | 80 |
| 5 | ♂ Nakami | 63 | Recurrence of Gastric Cancer | Close-irradation 2-fields Per field 600x5=3000r | 15 days | Stomach &Intestine Anastomosis | -ditto- | A mucinous Carzinoma. Cancerous cells observed | $X_1$ or $X_2$ | 16A |
| 6 | ♂ Abe | 57 | Gastric Cancer | -ditto- | 18 days | Curative resection | -ditto- | Adeno Carzinoma. Nuclear division picture observed. Poor effect | $X_1$ | 96A |
| 7 | ♂ Shinshaku | 67 | -ditto- | -ditto- | 18 days | -ditto- | Borrmann Type II | Squamous. Proliferation of squamous observed in the tissues underneath the mucous membrane. Nuclear division partly observed | $X_1$ | 100A |
| 8 | ♂ Takamura | 67 | -ditto- | -ditto- | -ditto- | -ditto- | Borrmann Type III | Adeno- Carzinoma. Nuclear division observed in cancerous cells | $X_1$ | 103 |

twenty years ago as already stated. At present, it is difficult to expect any success without obtaining possitive combined assistance of surgeons, pathologists and biochemists to use this method clinically. For this reason, we have had a group so-called "Hiroshima Cancerous Study Group" as our collaborator. The members of this group have always spare no benefical critisms and cooperations towards us.

The specimen of tissues extirpated by surgical intervention at two weeks intervals after the completion of pre-operative irradiation, will be examined by mid-operative examination specimen with a Cryostat (an equipment to be used for dissecting frozen tissues)and by the permanent specimen which are produced at Takeuchi Surgery. That is, this author asked for some decision and instructions to Dr. Monzen and Dr. Tokuoka, both pathologists, who also belong to the aforementioned study group, and also the special instruction was offered by Professor Takizawa of Chiba University, a respective teacher of Dr. Takeuchi.

For the readers' reference, the number of cases will be shown among over sixty cases of the pre-operative irradiation. (See Fig. 3)

This author received the following summarizing instructions from Professor Takizawa, that is,

"Concerning the results of pre-operative irradiation, the effect is still remained for Fujita, the Case No. 2. Cases No. 1 and 7 shows slight effects, while Case No. 6 shows almost no effect remained. Case No. 4 is not clear enough whether it is a cancer since several days elapsed after completion of irradiation, and it is necessary that this point should bear in mind".

Perusing through the above opinion, it is considerable that the effect of pre-operative irradiation is generally applicable to the Professor Takizawa,s judging criterion $X_1$ (Proliferation still observed) and the Case No. 4 may be applicable to $X_2$ or $X_3$ by observing from its clinical process. Consequently, the pre-operative irradiation for gastric cancer by close-irradiation (body cavity tube) and the common high voltage irradiation methods as we practised shows a slightest effects. However, as previously stated, we are obtaining a numerous clinical remarkable results which is unable to construe at present stage at least only by the past experiences.

## Chapter IV. Summary and Discussion

As it was observed in the results of examination, it is understood that the removed gastric cancer tissuses completed with the pre-operative irradiation is generally applicable to the $X_1$ of Professor Takizawa's judging criterion. That is, the aforementioned findings can be stated, such as, the nucleus was observed with indirect-division and multi-type, and the protoplasm was basic with multiform, which partly showing a change of vacant-tissue as well. However, it was clear enough to recognize that they were the histological pictures which might have caused again the proliferation by expiring of irradiation effect with lapse of time, and they have been cleared in details at the summary of previous

chapter as instructed by Professor Takizawa.

According to the effect shown in the various literatures, the above histological pictures are undoubtedly the judgement of imcomplete effect. Consequently, considering upon the histological effect judging criterion, it is very natural that our irradiation method and terms should also require immediate re-examination. Yet, we are not considering at all either to change our method or to give more influence upon cancer cells by putting any consideration for its terms, It is esteemed that this reason may be clear enough by our cherished opinions as frequently stated, but our irradiation method and terms have been contrived by considering the anti-cancerous condition of individual with cancer based on the radiobiology and cancer-immunity theory.

According to the predecessor's reports being noted in the various documents, the histological pictures of extirpated cancer tissues are extremely fine when it applies to the aforementioned judging criterion. However, the loss of appetite, nausea, feeling of weakness and loss of weight, such as they have been considered as the subjective and objective symptoms for individual with cancer at mid-irradiation, so-called clinical reaction, are not the clinical symptoms at least improved by therapeutic treatment. It is entirely counter state that the clinical symptoms before pre-irrediation, as stated in the earlier report, which showed a remarkable improvement at mid and post-irradiation. Such unfavourable clinical influences were nothing but provisional reactions caused naturally by over-irradiation of X-ray or Cobalt 60 gamma rays. However, as we previously stated, the clinical significance of pre-operative irradiation should not be only the reduction and/or resolution of the tumor but every clinical symptoms must be improved day after day. That is, the increase of appetite, every complained symptoms such as pains, nausea, passage troubles should be resolved and so-called "comfortableness" must be regained by irradiation. It is just because the "surgical intervention" which is to be thought as a biggest shock amongst a line of treatment schedule is in ahead of the cancer patients after the pre-operative irradiation.

In the pre-operative irradiation by $^{60}Co\gamma$. it cannot be expected and comfortableness even at my clinic as were experienced by roentgenic irradiation. However, we proved a success to prevent any marked unfavourable influence, as we see in the predecessor's reports, by determining the irradiation field and considering the irradiation doses. Naturally, the reduction of tumor can be succeed 100 per cent, and we determine the application for irradiation depending on the state of tumor.

In the cases of pre-operative irradiation by common high voltage and close-irradiation, the clinical symptoms will be improved only few days after the beginning of irradiation, as stated, and it is usual that almost in all cases the patients make such pleasant complaints "Should I still have an operation though I became so well like this?".

At such instances, either the result of blood test and the change of NPN amount in blood will be transited by showing the original value or even exceeds the original value within 1-2 weeks after irradiation, and they are not the testing value as we experienced

at the unfavourable prognosis at last stage of cancer cases.

When we consider combinedly that the cancer is not only the partial disease by tumor but it is the disease to control the whole body elements of the individual with cancer, and the therapeutic treatment is not only the primary local effect of radiation but it is the combined action to be affected for whole body with the secondary biological effect by cancerous necrohormones, it must be considered that both factors, that is, the improvement of clinical symptoms and the reduction of tumor should be adapted into the effect judging criterion.

For the above reasons, we are unable to change our present method even though the degree of disorder of our histological pictures are to be considered as the degree of $X_1$. If, the irradiation eftect of $X_2$ and $X_3$ are further necessary without breaking down our method and terms, then, we do not hesitate to take into consideration of the extension of irradiation period and increase of dosage for per irradiation from the radiological point of view.

It must be realized that the cancer which has developed to a certain extent is hard to expect for complete cure by only applying a large dose to the primary cancer. It is needless to say that the most essential clinical significance for pre-operative irradiation is to reduce the size of primary cancer by pre-operative irradiation and, to establish anti-cancerous condition in the whole body by cancer necrohomones, which is to be considered as the products of destroyed cancerous cells. The next important fact is that as many denaturalization and/or disruption of cancerous cells as possible will cause favourable results such as to raise safety degree for surgical intervention. If so, there is a need of proper " balance " between the establishment of anti-cancerous condition and disruption of cancer tissues, and we cannot say that it is always good for the individuals with cancers even though the $X_2$ and $X_3$ effects are indicated. Or, does not it cause rather excessive product of cancer necrohormones? Observing this upon the numerous cases of predecessors reports, it seems to be that the aggravation of clinical symptoms have been related to this. Also, it is considerable that excessive cancer necrohormones which may produce abruptly accordidg to the development of disruption towards $X_2$ and $X_3$ is may be fortunately cause favourable result by early extirpation of primary cancer. For instance, when various reaction are considered, such as the pre-operative irradiation strongly affects to the sub-kidney functions, it naturally holds a theory of the necessity to conduct surgical intervention immediate after the irradiation of large doses, and that they were already explained as the secondary method of pre-operative irradiation.

It is needless to mention that the treatment results of cancer are remarkably different according to the nature of cancer and its site of occurrence, and the irradiation method and condition should be different accordingly. However, this is not a proper time to discuss about the effect as wholly, so I shall make thorough inquiries for the essential terms at the first stage of pre-operative irradiation upon the knowledge obtained from histological pictures, that is, (1) applicable dosage for irradiation (2) problems to

determine the period for surgical intervention (3) method of effect judgement, etc.

First of all, a review on the applicable dosage for irradiation may be explained. Approximate doses applicable for irradiation for the inoperable and/or recurrence cancer cases will be between 2,000r and 3,000r which is the doses to be computed from our many years' irradiation experiences and results of experimental studies on the radiological standpoint. Also, if focus dose exceeds over 30% per dose, there will be more or less the process by sensibility difference of cancer cells, however, it is usual that the denaturalization and/or reduction may occur from 3 to 5 days after the begining of irradiation. When whole doses irradiated (if focus dose of over 600–1,000r is reached), the denaturalization of cancer cells will be developed everyday as time goes by. However, for the cancer cells, any marked denaturalization is hard recognizable histologically, and the reduction of "living power of cells" is clearly knowable upon its "energy metabolism".

In my experimental studies regarding to the effects of X-ray affected upon the substance metabolism of malignant tumor, the value of the organic tissue respiration and glycolysis of tumor, which was exercised combinedly with the metabolism of salts and energy metabolism of viscera organs, had shown the following important indications.

That is, this author had transplanted the tumor on the back of rabbit by using the transplantable Kato strain rabbit sarcoma, and when it bedded on and developed to a size of thumb-tip approximately between 15 and 20 days after transplantation conducted a full dose of 3,600r was applied in nine consecutive days (400r at a time) and thus, I thoroughly investigated the progress basing on the value of pre-irradiation.

As it was observed for the result, the tissue respiration (henceforth describe as $QO_2$) before irradiation indicated average-9.2 had reduced to-2 on first day, while the glycolysis effect (henceforth describe as $Q_M^{N_2}$) indicated average 29.2 showed a sudden drop 8.2, and on the third day, they further dropped violently such as-1.2 for $QO_2$ and 4.5 for $Q_M^{N_2}$. Although this low value showed more or less unsteadiness for about a week or two, it was sustained. That is, at first week, $QO_2$ had indicated-2.0 while $Q_M^{N_2}$ was 6.7, on second week--1.8 for $QO_2$ and 5.2 for $Q_M^{N_2}$ and the thorough investigation was made accordingly with lapse of time which later showed-3.0 for $QO_2$ and 18.4 for $Q_M^{N_2}$ on the fifth week. However, when it entered into the tenth week, it showed-7.3 for $QO_2$ and 26.8 for $Q_M^{N_2}$, of which, indicating an increase on a part of tumor, and was observed a peculiar "energy" metabolism as the malignant tumor cells. As for the non-irradiated tumor, it was indicated-4.7 for $QO_2$ and 15.7 for $Q_M^{N_2}$ on first week after the completion of irradiation, which was clearly affected with the remote effect of cancer necrohormones, while on second week, it was observed that-4.7 for $QO_2$ and 16.8 for $Q_M^{N_2}$, which still showed nearly 50% of "shock".

We used the words of "establishment for anti-cancerous condition by pre-operative irradiation" considering upon the facts of the organic respiration and glycolysis of livers and spleens of the individuals with cancers, as previously stated in my second report relating this study, which showed the remarkable restoration far exceeded the normal value betweend 1st and 2nd week after the completion of irradiation, together

with their results. This concept was based on the state of energy metabolism of malignant tumor and the state of restoration of energy metabolism of vital viscera organs.

In the above experiment, the cells surrounding the border of tumor were completely disrupted and resolved two weeks after the completion of irradiation at a full dose of 3,600r, and they were replaced in the combined tissues which was impressed as if they covered the group of inner cancer cells. Observing this tissue as a whole, the normal cells of tumor were possible to sight in the center of tumor and we had experience the instances as they were also transplantable. Considering these facts, there were some instances seems to be contradictory that the cancerous tumor was judged to be dangerous histologically which should have been judged as cured clinically.

Although we admit that the irradiation effect judging criterion for cancer substance originated by Professor Takizawa is worthwhile guide for determining the proper dosage for the pre-operative irradiation of today, we firmly believe that we will be possible to obtain favourable results at present stage even though the effect judgement is considred as $X_1$. That is, our theory is consisted of the aforementioned energy metabolism of cancer cells and biological experiences of the individuals with cancers.

By considering the clinical symptoms of the individual with cancer, we are also putting forward our studies in the field of physic-engineering on the radiological standpoint as to make an attempt for the improvement of its effect towards $X_2$ and $X_3$, if necessary.

Next, the decision of surgical intervention period should be considered as secondary important term which is the subject to control the result for cancer treatment program. As it is now well understood, we have fixed the period of 10 to 15 days after the completion of irradiation as for the first method of the pre-operative irradiation, and as for the secondary method, it was set immediate after the irradiation. Considering upon the radiobiological and cancer immunological view-point about the individual with cancer, this selection of intervals would be quite natural.

Although it drew our particular interest on what ground the predecessors have decided the surgical intervention period, we were able to learn that their method had been fixed upon the professor Takizawa's irradiation effect judging criterion according to the various reprints and documents. For example, even at the instance of large dose irradiation of over 3,000r they had encountered with the cases shown proliferation ($X_1$) of cancer cells, and they reported that the investigation of the results by histological pictures had revealed that they caused by the postponement (from 2 to 7 weeks after the completion of irradiation) of surgical intervention period. It is also described that the radical operation should be performed immediate after the completion of irradiation and/or within a week, otherwise, it may causes the recurrence of cancer.

However, as it was previously stated, even if the surgical intervention period is to be postponed to a maximum of 7 weeks at the case of large dose irradiation of over 3,000r,

there will be no notable evil affect occur to the individual with cancer in case the improvement is made as we clinically confirmed. In favourable clinical symptoms, this degree of postponement is rather advantage, and it should be considered that the proper production of cancer necrohormones will be performed. As a matter of fact, we believe it is quite natural that a certain intervals should be placed upon the fact of energy metabolism of cancerous cells, as mentioned above.

Nevertheless, if the clinical symptoms become worse in such cases and also the tumor become proliferated and aggravated, the fault is not either the decision of surgical intervention period nor the individual, but it is the problem of the method and terms of irradiation whether the 3,000r was proper dose or not. It should be construed that inappropriate irradiation exerted evil influence to the whole body of the individual and impeded anti-cancerous condition, and furthermore, caused the deterioration of immunity of whole body and irradiated region accordingly. However, it draws our particular attention to learn the fact that from 30 to 40 per cent of the cases so-called "ineffectiveness" were reported since therapeutic treatment by $^{60}Co\gamma$ had begun in recent times. Regarding this point, this author already pointed out in the previous thesis that, in fact, so-called "karzinomreizdosis" in ancient ages were in excess of amount which might be caused the countereffect. It is just because I remember that the ineffective cases at the time of poor energy in the past was primarily bounded to the inapplicable cases only. On other hand, the dangerous to decide the surgical intervention period only by the histological pictures hold the following reasons.

As aforementioned, even though the morphological change of cancer cells is either constant or gives further proliferation pictures, the energy metabolism will be maintained its unusual metabolism which at once clearly deteriorated extending over five weeks, and that we further learned it deteriorated violently within 1-2 weeks. An essentiality of time factor at this radiobiological effect is not only bounded to the mid-irradiation but it should be considered even at the post-irradiation. Thus, the cancer necrohormones will gradually occur and affect according to the Arndt-Schultz Law. However, in the words so-called "degree of radiation sensibility for cancer cells" does not only mean the direct sensibility against radiology but it means the sensibility against cancer necrohormones, and we should always bear in mind this fact at the lapse of time in post-irradiation.

Accordingly, the time which proper dose of cancer necrohormones brings the individual with cancer to the most fitted anti-cancerous condition, then it will be the time of emergency for cancer cells due to sensibility against cancer necrohormones, and the incividual with cancer will be placed in the most suitable time for surgical intervention.

At the time factor between 10 and 15 days after the completion of irradiation, the energy metabolism cancer cells will become minimum; the remote-effect of cancer necrohormones will cause 50% deterioration to the energy metabolism of non-irradiated cancer; the substance metabolism will restore to the former condition; the essential

viscera organs such as livers and spleens, etc, participating the immunity of individual with cancer will show acceleration of energy metabolism and so on, thus, our clinical observation will be resumed the usual "comfortableness" as stated, which agrees for clinically to the best time after completion of irradiation. Several radiological energies which were not freely obtainable in the past as today, the effect of therapeutic treatment was not much expected as it was feared the various post-disorders by radiation except some results were obtained in the pre-operative irradiation for breast cancer. However, at present, it became an era which had been affirmed as there is almost no hindrance for surgical intervention even though a large dose for a long time to be applied, which, no one ever anticipated in the past. Consequently, a large dose should be applied for a long time in attaining the improvement of irradiation effect (X). Yet, it is needless to discuss, even to this, a certain limit or the optimum is being existed.

Two opposite terms, which, the cancer cells should be removed of the individual as early days as possible, on other hand, the radiological irradiation should be applied as long as required, must be accomplished at this place.

While on considering to solve this problem, we have come to experience the exceptional effect of cancer necrohormones which brought us the first method of pre-operative irradiation and subsequently, the therapeutic transplantation of extirpated cancer tissues was realized.

Nevertheless, the fact that this also conform with the theory of cancer immunity is one of the reason why we have more confidence for this therapeutic treatment schedule.

Upon concluding this manuscript, this author wish to express a heartfelt thanks to Professor Takizawa, The Medical Department of Chiba University, who consistently gave me the special directions and instructions.

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